REMARKS

Claims 1-11, 14-25, 28-42, 44-55, 57-67, 69-94, 96-108, and 111-118 are pending. Claims 12-13, 26-27, 43, 56, 68, 95, 109-110, and 119-120 have been cancelled.

The amendments specifying that some operations be performed automatically are supported at various locations in the specification. See for example, page 9, lines 7-15. Other amendments find support throughout the specification and in some of the originally submitted claims. See for example original claims 43 and 74.

The Bacus patent is used to reject claims 1-37. The Zhu patent is used together with Bacus to reject the remaining claims. The rejections of claims 38-100 will be addressed first. As indicated, these claims were rejected by a combination of Bacus and Zhu. All method claims in this group recite "from the image, automatically extracting values of one or more mitosis indicator parameters that correspond to a cell division state of the cell." The computer program product claims and apparatus claims recite similar features.

Bacus describes a tool for helping medical personnel (e.g., pathologists) classify cells using microscopy and limited image analysis. It appears to allow a form of automated ploidy analysis, in which the system measures the optical density of stained DNA in a cell-by-cell manner. It converts the measured optical properties to DNA mass. It does not disclose any sort of "mitosis indicator parameter" and the Examiner does not use it for that purpose.

Zhu presents the sequence and some characteristics of mitosin, a protein said to be necessary for a cell to enter the M phase and necessarily absent (or degraded) for a cell to proceed from the M phase to the next stage. (See the abstract and the summary beginning at column 1, line 44.) The cited sections of Zhu are silent on any form of automated analysis of images. While images of mitosin within cells could possibly be used in the automated methods of the present invention to facilitate cell cycle classification, Zhu provides no suggestion of how this would be accomplished or even that it would be desirable. In fact, the Zhu reference itself does not suggest any image analysis other than a human interpreting and classifying images of cells showing mitosin.

The relevant claims are directed to an automated analysis of images. Specifically, some of claims 38 et seq. recite (i) from the image, automatically extracting values of one or more

mitosis indicator parameters that correspond to a cell division state of the cell; and (ii) automatically classifying the cell as either mitotic or interphase based upon (at least) the extracted values of the one or more mitosis indicator parameters.

Neither cited reference approaches these concepts. The intracellular presence of mitosin protein is said to be an indicator of mitosis, but the cited portions of Zhu fail to explain or suggest that it should be used in any sort of automated image analysis – either for extracting a mitosis indicator parameter or for classifying the cell according a cell cycle state. Merely describing and imaging an interesting cellular component that is tied to mitosis is insufficient to suggest either "automatically extracting (from an image of a cell) values of one or more mitosis indicator parameters" or "automatically classifying the cell as either mitotic or interphase based upon the extracted values . . . ."

Applicants note that the examiner has cited Zhu (column 1, lines 61-66, column 4, lines 17-27, and column 19, lines 25-35) for disclosing "from an image, extracting values of one or more mitosis indicator parameters that correspond to a cell division state of the cell." The identified sections pertain to an RNA blotting analysis (figures 1A and 1B), an image of mitosin-stained cells (figure 10), and a description of a flow cytometry study, respectively. None of these pertain to any form of automated analysis of an image of a cell. In fact, only the description of figure 10 pertains an image of a cell. Neither the RNA blotting analysis nor the flow cytometry passages pertain to images of cells. Bacus, for example, points out that flow cytometry "does not allow for the analysis of morphological features of cells . . . ." See column 2, lines 25-29.

Applicants also note that the examiner cites Zhu (column 4, lines 48-58 and column 16, lines 60-63) as disclosing "classifying the cell as either mitotic, or interphase based upon the extracted values of the one or more mitosis indicator parameters." The identified sections pertain to (i) a description of the perceived function of mitosin in the progress of a cell through mitosis and (ii) a mention that "the mitotic stages of cells described above were determined by DAPI staining of nuclear DNA." Again, neither cited section suggests any form of automated image analysis. Cell biologists long ago learned how to distinguish stained cells in various stages of the cell cycle. However, the invention pertains to image analysis methods that automatically extract specific information from cell images and classify cells based on inventive parameters and analyses described and claimed in the present application.

It is believed that claim 38 and its dependent claims (39-50), as well as claims 51-72, are patentable for at least the reasons presented above. Withdrawal of the rejections is respectfully requested.

Dependent claim 44 recites a "statistical variance in DNA concentration within the cell" as a specific mitosis indicator parameter. The Office rejected claim 44 on the basis of Zhu's description at column 19, lines 25-31.

> To elucidate the effect of the overexpression on cell-cycle progression, CV1 cells were analyzed by two-parameter flow cytometry three days after transfection. As summarized in Table 1, cell fractions with 4N DNA content (G2/M phase) were largely increased and those with S phase DNA content were variably decreased in cells expressing any of the five constructs compared to non-expression populations.

The constructs referenced here are mutant forms of mitosin chosen to elucidate the physical association of mitosin with the kinetochore/centromere. The research described here has nothing to do with automated analysis of cell images. It involves flow cytometry to characterize cells based on the amount of DNA. As indicated above, flow cytometry does not employ images of cells. It is therefore respectfully submitted that claim 44 is patentable over the cited art. Note that the "variance" in claim 44 is a statistical parameter. This has been made explicit by amendment.

Claims 78-100 are also patentable. These claims are similar to claims 38-77 in that they recite automatically extracting values of one or more mitosis indicator parameters of the types described above and classifying a cell using that information. In addition, these claims recite that the classifying is done using both the total amount of DNA and the one or more mitosis indicator parameters. The combined use of the total amount of DNA in a cell and a mitosis indicator parameter is nowhere suggested in the cited art. It is respectfully submitted that claims 78-100 are patentable for at least the reasons set forth above. Note that claims 74, 75 and related dependent claims have been amended to clarify that the recited operations actually discriminate between the various cell cycle stages identified in those claims. An automated image analysis method for accomplishing this is nowhere disclosed or suggested in the cited art.

Claims 101-120 pertain to a computer related invention that employs cell images for a population of cells to provide information allowing determination of parameters for classifying cells. These parameters may then be used, for example, to automatically classify cells in subsequent studies. In other words, the claims in question describe an invention to facilitate development of models, algorithms, or other tools for use in classifying cells into particular stages of the cell cycle. Thus, the parameters identified in claims 101-120 can be used in methods and systems such as those described in claims 73-100. Note that claims 101-120 recite use of both a mitotic discriminator (as described above) and the amount of DNA in cells in determining the parameters to be used in subsequent classifications of cells in the cell cycle.

It is respectfully submitted that nothing of the sort is suggested in the cited references. Withdrawal of the rejections of claims 101-120 is respectfully requested.

Applicants wish to make a final comment about the propriety of combining the cited references. The Action argues that the teachings of Bacus and Zhu are properly combinable in making a rejection under section 103. Assuming for the sake of argument that the references are properly combinable, Applicants respectfully submit that the claimed invention is not in any way discernible from such combination, absent picking and choosing features recited in the claims and then arranging those features in the manner claimed. To select and arrange the claim elements requires multiple non-obvious leaps, including selection of particular mitosis indicator parameters, developing a method that automatically extracts these from an image of a cell, and inventing a method for automatically classifying a cell into a particular state associated with cell cycle based upon the information extracted from an image of the cell.

Finally, claims 1-37 were rejected on the basis of Bacus alone. These claims have been amended to recite automatic extraction of a mitosis indicator parameter and to automatically determine whether a cell is in a particular cell cycle state using an image of the cell. These claims are believed patentable over the cited art for various of the reasons set forth above. Withdrawal of the rejections of claims 1-37 is respectfully requested.

Applicants believe that all pending claims are allowable and respectfully requests a Notice of Allowance for this application from the Examiner. Should the Examiner believe that a telephone conference would expedite the prosecution of this application, the undersigned can be reached at the telephone number set out below.

Respectfully submitted,
BEYER WEAVER & THOMAS, LLP

Jeffrey K. Weaver
Reg. No. 31,314

P.O. Box 778
Berkeley, CA 94704-0778
(510) 843-6200